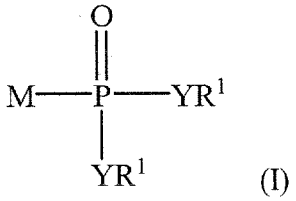
In the Claims

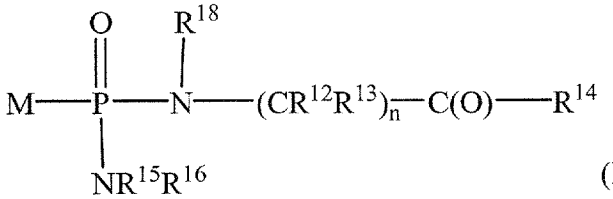
1-94 (canceled).

95 (currently amended). A method of treating a mammal having diabetes comprising the administration to said mammal a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrug or salt thereof, wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA);

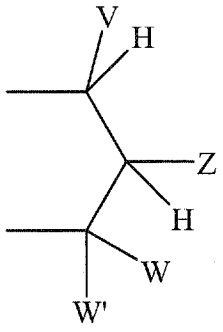
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-$C(O)R^3$, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, up to containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower aryl, substituted or unsubstituted lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

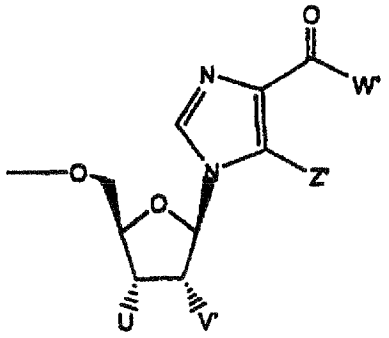
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$ and:

M is



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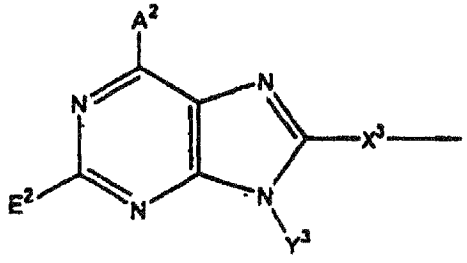
wherein

Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino; or

M is



,

wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of –H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

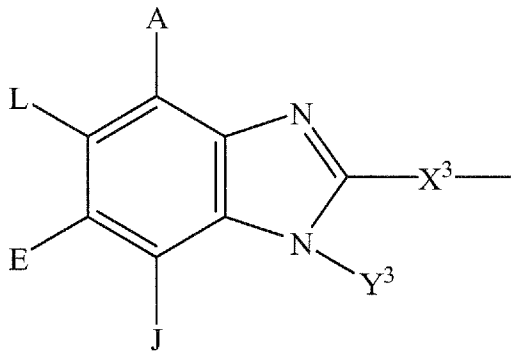
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; or

M is:



,

wherein:

A, E, and L are selected from the group of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

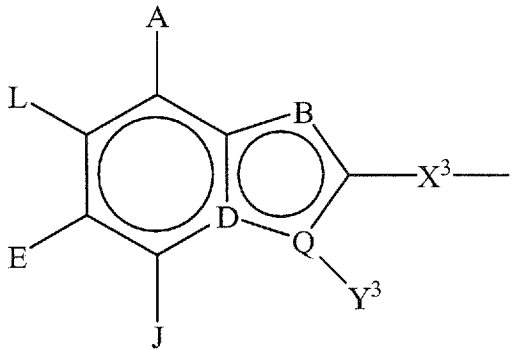
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $–C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $–OR^2$; or

M is:



,

wherein

B is selected from the group consisting of –NH-, -N= and –CH=;

D is selected from the group consisting of $—\overset{|}{C}=$ and $—\overset{|}{N}—$;

Q is selected from the group consisting of –C= and –N- with the proviso that when B is –NH- then Q is –C= and D is $—\overset{|}{C}=$, when B is –CH= then Q is –N- and D is $—\overset{|}{C}=$, when B is –N=, then D is $—\overset{|}{N}—$ and Q is –C=;

A, E, and L are selected from the group of $–NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $–NR^8{}_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl,

aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $–COOR^2$, $-SO_3H$, or $–PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $–OR^3$, all except H may be substituted;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

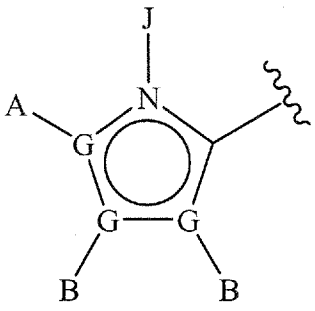
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $–C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

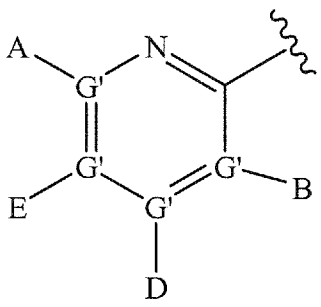
R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $–OR^3$; or

M is



or



,

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that all groups except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that all except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $–COOR^2$, $-SO_3H$, or $–PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $–OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, substituted or unsubstituted –alkyloxy-, or substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups.

96 (previously presented). The method of claim 95 wherein said insulin sensitizer is a thiazolidinedione.

97 (previously presented). The method of claim 96 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

98-119 (canceled).

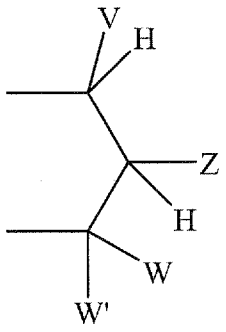
120 (currently amended). The method of claim 95 wherein M is R^5-X-;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is -NR^6-, then R^1 attached to -NR^6- is independently selected from the group consisting of -H, -$[C(R^2)_2]_q$-$COOR^3$, -$C(R^4)_2COOR^3$, ~~-$[C(R^2)_2]_q$-C(O)SR,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

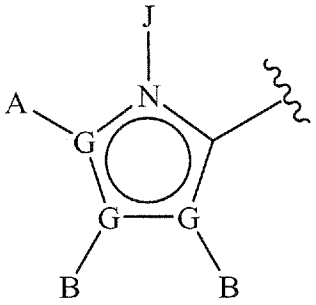
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

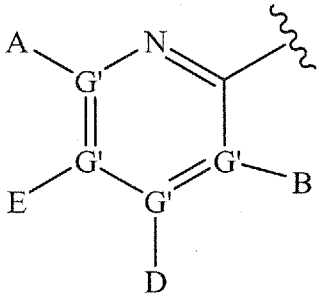
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



,

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4

and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,a~~linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups and pharmaceutically acceptable salts thereof.

121 (original). The method of claim 120 wherein said insulin sensitizer is a thiazolidinedione.

122-123 (canceled).

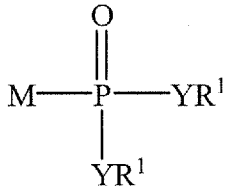
124 (original). The method of claim 95 wherein said combination is administered orally.

125 (previously presented). The method of claim 95 wherein said combination is administered separately during the day.

126 (previously presented). The method of claim 95 wherein said combination is administered simultaneously during the day.

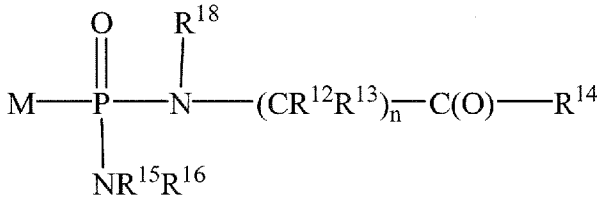
127 (currently amended). A method of treating a mammal having a disease characterized by insulin resistance and/or hyperglycemia comprising the administration to said mammal an

effective amount of an insulin sensitizer agent and an FBPase inhibiting amount of an FBPase inhibitor, wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA);

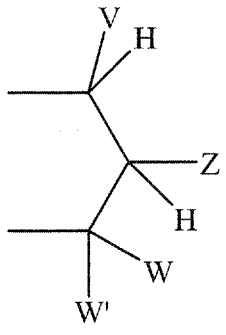
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$~~, and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, up to containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower aryl, substituted or unsubstituted lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

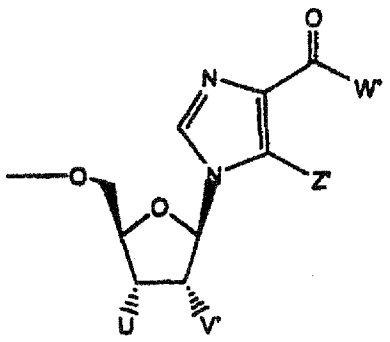
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and:

M is



,

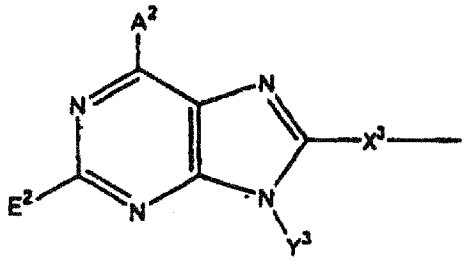
wherein

Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino; or

M is



,

wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of –H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

–alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $–COOR^2$, $-SO_3H$, or $–PO_3R^2_2$;

Y^3 is selected from H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $–OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

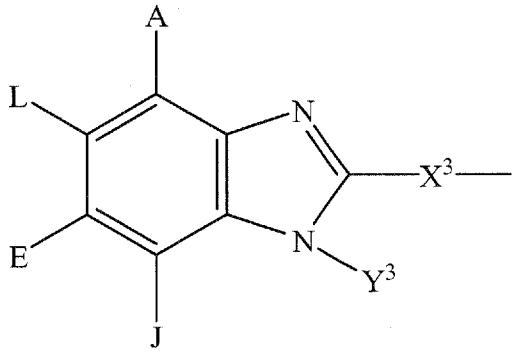
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $–C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $–OR^2$; or

M is:



,

wherein:

A, E, and L are selected from the group of $–NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or

together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

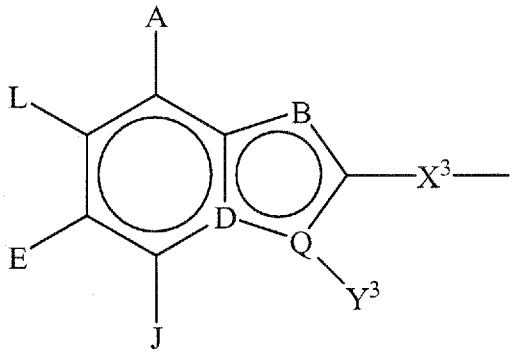
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$; or

M is:



,

wherein

B is selected from the group consisting of –NH-, -N= and –CH=;

D is selected from the group consisting of $-\overset{|}{C}=$ and $-\overset{|}{N}-$;

Q is selected from the group consisting of –C= and –N- with the proviso that when B is –NH- then Q is –C= and D is $-\overset{|}{C}=$, when B is –CH= then Q is –N- and D is $-\overset{|}{C}=$, when B is –N=, then D is $-\overset{|}{N}-$ and Q is –C=;

A, E, and L are selected from the group of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H may be substituted;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

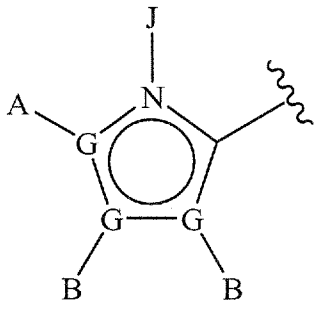
R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

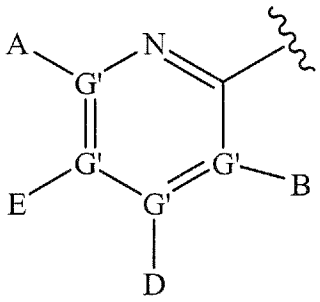
R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^3$; or

M is



or



,

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, $-CN$, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that all groups except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that all except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, substituted or unsubstituted –alkyloxy-, or substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups.

128 (previously presented). The method of claim 127 wherein said disease is characterized by insulin resistance.

129 (previously presented). The method of claim 127 wherein said disease is characterized by hyperglycemia.

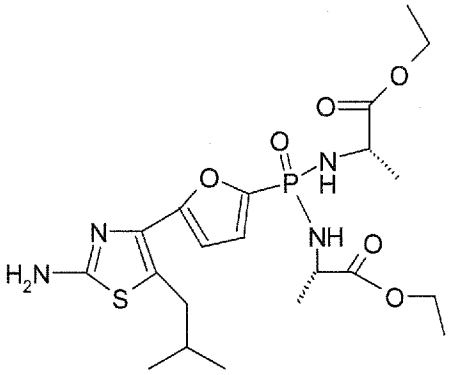
130 (previously presented). The method of claim 127 wherein said disease is obesity.

131 (previously presented). The method of claim 127 wherein said disease is hypertension.

132 (previously presented). The method of claim 127 wherein said disease is polycystic ovarian syndrome.

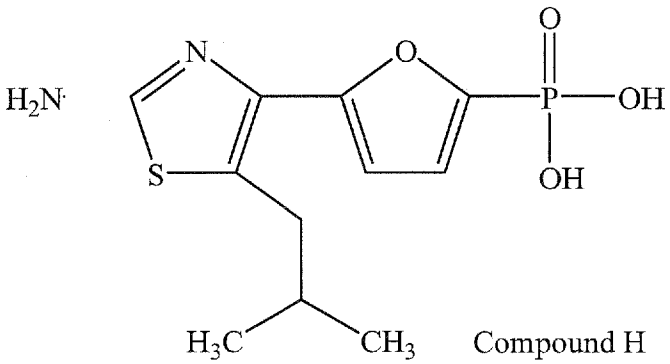
133-146 (canceled).

147 (previously presented). The method of claim 95 wherein said FBPase inhibitor is



Compound J

or

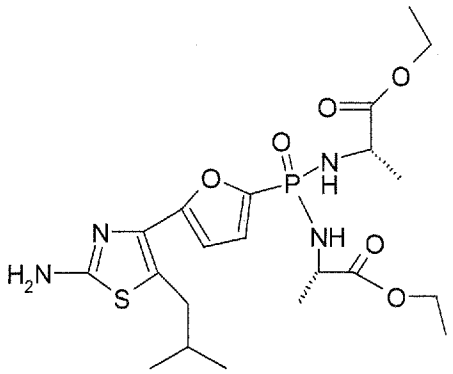


Compound H

and said insulin sensitizer is troglitazone.

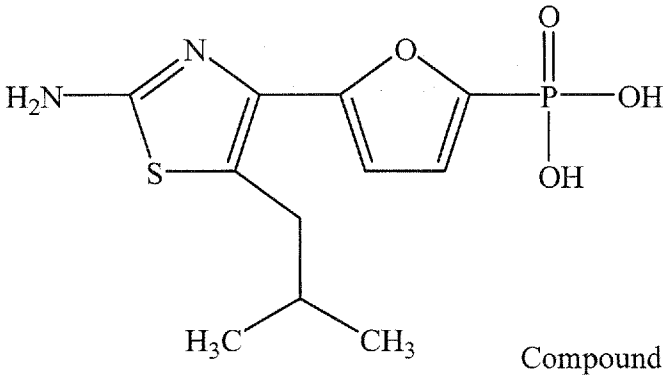
148-150 (canceled).

151 (previously presented). The method of claim 127 wherein said FBPase inhibitor is



Compound J

or

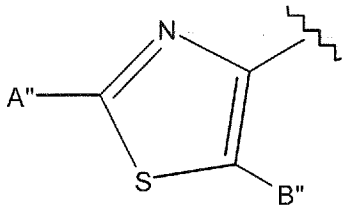


Compound H

and said insulin sensitizer is troglitazone.

152-167 (canceled).

168 (previously presented). The method of claim 120 wherein R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, provided that any group except -H, -CN, perhaloalkyl, and halo may be substituted.

169 (previously presented). The method of claim 168 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and provided that any group except -H and halo may be substituted.

170 (previously presented). The method of claim 169 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

171 (previously presented). The method of claim 120 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

172 (previously presented). The method of claim 171 wherein X is furan-2,5-diyl.

173 (previously presented). The method of claim 120 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

174 (previously presented). The method of claim 173 wherein both Y groups are -O- and R^1 is H.

175 (previously presented). The method of claim 120 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q$-$COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q$-$C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

176 (previously presented). The method of claim 175 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

177 (previously presented). The method of claim 168 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

178 (previously presented). The method of claim 168 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

179 (previously presented). The method of claim 168 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

180 (previously presented). The method of claim 168 wherein X is furan-2,5-diyl and YR^1 is OH.

181 (previously presented). The method of claim 168, wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

182 (previously presented). The method of claim 168, wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

183 (previously presented). The method of claim 182 wherein X is furan-2,5-diyl.

184 (previously presented). The method of claim 168 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

185 (previously presented). The method of claim 184 wherein X is furan-2,5-diyl.

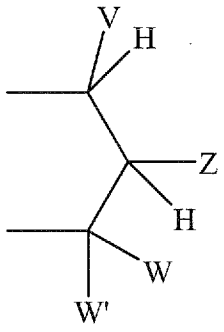
186 (currently amended). The method of claim 95 wherein said insulin sensitizer is a thiazolidinedione and M is R^5-X-;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is -NR^6-, then R^1 attached to -NR^6- is independently selected from the group consisting of -H, -$[C(R^2)_2]_q$-$COOR^3$, -$C(R^4)_2COOR^3$, ~~-$[C(R^2)_2]_q$-C(O)SR,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or

together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is a substituted or unsubstituted group independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, all except H may be substituted, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

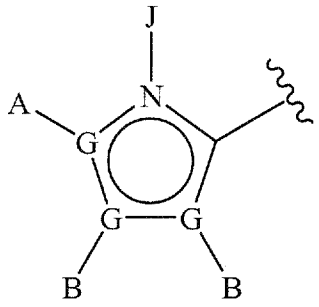
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

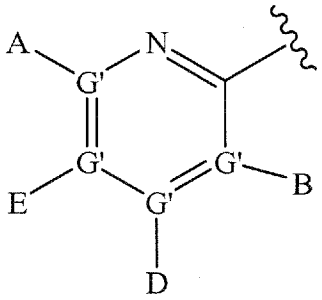
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, wherein any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, wherein any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is substituted or unsubstituted and is selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

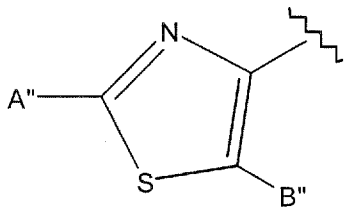
3) when R^5 is a six-membered ring, then X is not any 2 atom linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and

R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

187 (previously presented). The method of claim 186 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and any group except -H, and halo may be substituted.

188 (previously presented). The method of claim 187 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

189 (previously presented). The method of claim 186 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

190 (previously presented). The method of claim 189 wherein X is furan-2,5-diyl.

191 (previously presented). The method of claim 186 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

192 (previously presented). The method of claim 191 wherein both Y groups are -O- and R^1 is H.

193 (previously presented). The method of claim 186 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

194 (previously presented). The method of claim 193 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

195 (previously presented). The method of claim 186 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

196 (previously presented). The method of claim 186 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

197 (previously presented). The method of claim 186 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

198 (previously presented). The method of claim 186 wherein X is furan-2,5-diyl and YR^1 is OH.

199 (previously presented). The method of claim 186, wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

200 (previously presented). The method of claim 186, wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

201 (previously presented). The method of claim 200 wherein X is furan-2,5-diyl.

202 (previously presented). The method of claim 186 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

203 (previously presented). The method of claim 202 wherein X is furan-2,5-diyl.

204 (previously presented). The method of claim 186 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

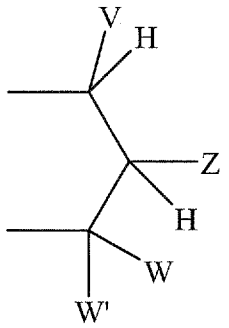
205 (currently amended). The method of claim 127 wherein M is R^5-X-;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is -NR^6-, then R^1 attached to -NR^6- is independently selected from the group consisting of -H, -$[C(R^2)_2]_q$-$COOR^3$, -$C(R^4)_2COOR^3$, ~~-$[C(R^2)_2]_q$-C(O)SR,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is a substituted or unsubstituted group independently selected from the group consisting of H, lower alkyl, lower aryl, and lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

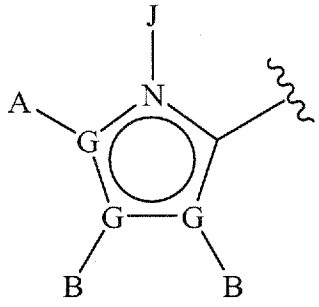
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

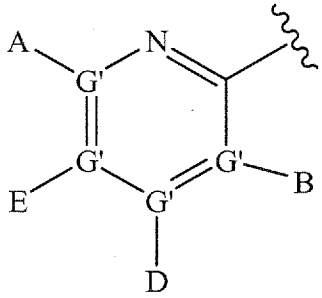
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, wherein any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, wherein any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

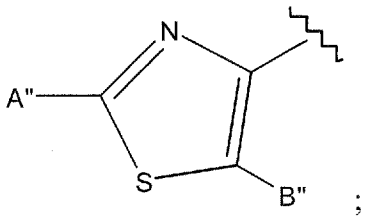
2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups.

206 (previously presented). The method of claim 205 wherein R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

207 (previously presented). The method of claim 205 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H and halo are may be substituted.

208 (previously presented). The method of claim 207 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

209 (previously presented). The method of claim 205 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

210 (previously presented). The method of claim 209 wherein X is furan-2,5-diyl.

211 (previously presented). The method of claim 205 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

212 (previously presented). The method of claim 211 wherein both Y groups are -O- and R^1 is H.

213 (previously presented). The method of claim 205 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q$-$COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q$-$C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

214 (previously presented). The method of claim 213 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

215 (previously presented). The method of claim 205 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

216 (previously presented). The method of claim 205 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

217 (previously presented). The method of claim 205 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

218 (previously presented). The method of claim 205 wherein X is furan-2,5-diyl and YR^1 is OH.

219 (previously presented). The method of claim 205 wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

220 (previously presented). The method of claim 205 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

221 (previously presented). The method of claim 220 wherein X is furan-2,5-diyl.

222 (previously presented). The method of claim 205 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

223 (previously presented). The method of claim 222 wherein X is furan-2,5-diyl.

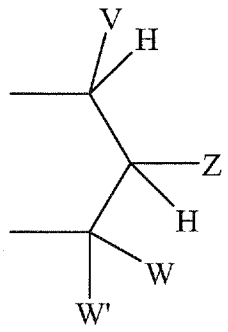
224 (currently amended). The method of claim 127 wherein said insulin sensitizer is a thiazolidinedione and M is R^5-X-;

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is -NR^6-, then R^1 attached to -NR^6- is independently selected from the group consisting of -H, -$[C(R^2)_2]_q$-$COOR^3$, -$C(R^4)_2COOR^3$, ~~-$[C(R^2)_2]_q$-C(O)SR,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form a substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is a substituted or unsubstituted group independently selected from the group consisting of H, lower alkyl, lower aryl, and lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

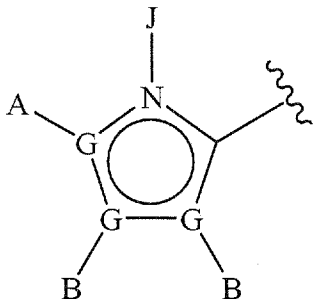
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

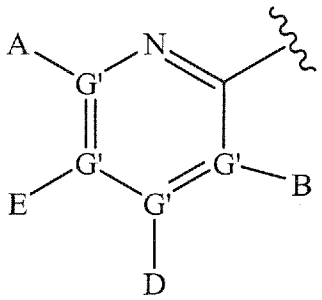
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, wherein any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, wherein any group except–H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

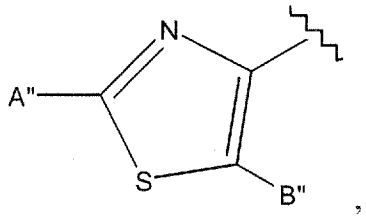
3) when R^5 is a six-membered ring, then X is not any 2 atom linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and

R^5 is



,

A'' is of -H, $-NR^4{}_2$, $-CONR^4{}_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4{}_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4{}_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9{}_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

225 (previously presented). The method of claim 224 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from–H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H and halo may be substituted.

226 (previously presented). The method of claim 225 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

227 (previously presented). The method of claim 224 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

228 (previously presented). The method of claim 227 wherein X is furan-2,5-diyl.

229 (previously presented). The method of claim 224 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

230 (previously presented). The method of claim 229 wherein both Y groups are -O- and R^1 is H.

231 (previously presented). The method of claim 224 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q$-$COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q$-$C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

232 (previously presented). The method of claim 231 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

233 (previously presented). The method of claim 231 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

234 (previously presented). The method of claim 224 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

235 (previously presented). The method of claim 224 wherein X is furan-2,5-diyl and YR^1 is OH.

236 (previously presented). The method of claim 224 wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

237 (previously presented). The method of claim 224 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

238 (previously presented). The method of claim 237 wherein X is furan-2,5-diyl.

239 (previously presented). The method of claim 224 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

240 (previously presented). The method of claim 239 wherein X is furan-2,5-diyl.

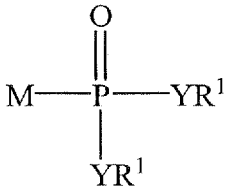
241 (previously presented). The method of claim 224 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

242-244 (canceled).

245 (previously presented). The method of claim 127 wherein said combination is administered orally.

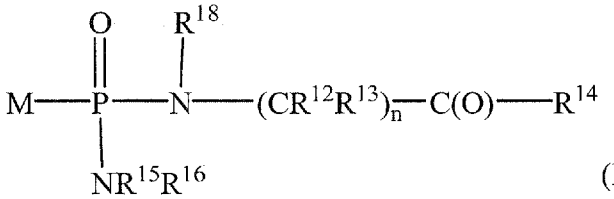
246-250 (canceled).

251 (currently amended). A method of treating impaired glucose tolerance comprising administering to patients in need thereof a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrugs or salts thereof, wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA);

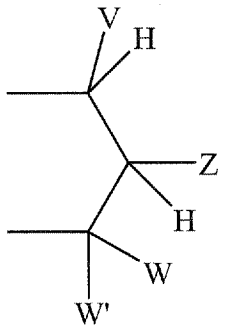
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, up to containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower aryl, substituted or unsubstituted lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

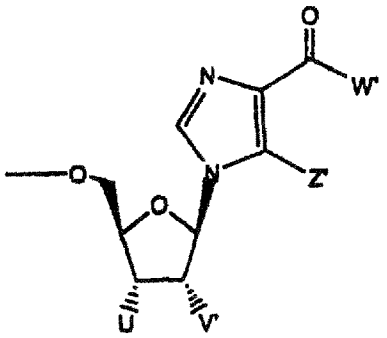
R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n-C(O)-R^{14}$, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected

from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$ and:

M is



;

wherein

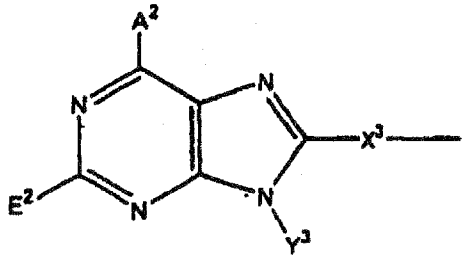
Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino;

and pharmaceutically acceptable salts thereof; or

M is



;

wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of –H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

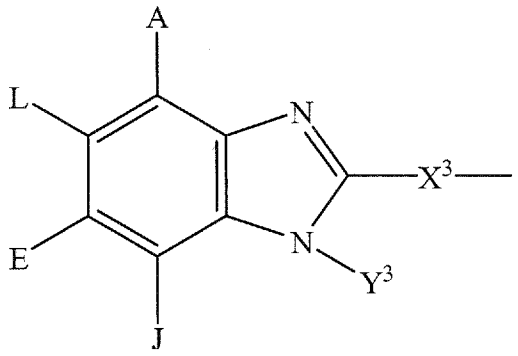
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein:

A, E, and L are selected from the group of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $–C(O)R^{10}$;

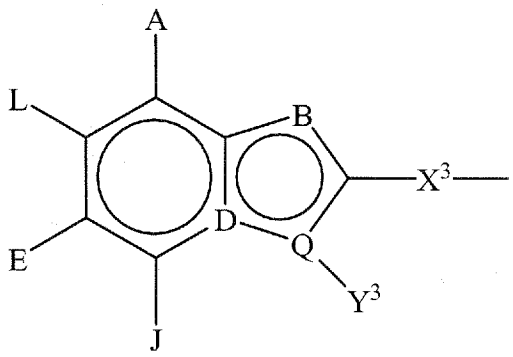
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $–OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein

B is selected from the group consisting of –NH-, -N= and –CH=;

D is selected from the group consisting of $—\overset{|}{C}=$ and $—\overset{|}{N}—$;

Q is selected from the group consisting of –C= and –N- with the proviso that when B is –NH- then Q is –C= and D is $—\overset{|}{C}=$, when B is –CH= then Q is –N- and D is $—\overset{|}{N}—$ $\underline{—\overset{|}{C}=}$, when B is –N=, then D is $—\overset{|}{N}—$ and Q is –C=;

A, E, and L are selected from the group of $–NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H may be substituted;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

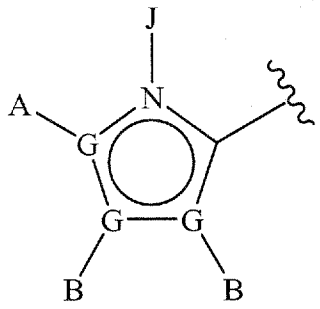
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

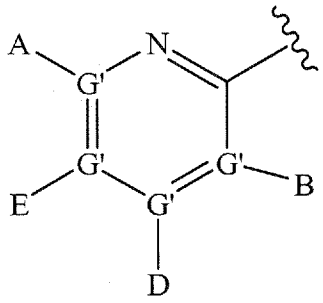
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^3$, and

pharmaceutically acceptable salts thereof; or

M is



or



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that all groups except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that all except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, substituted or unsubstituted –alkyloxy-, or substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

252 (currently amended). The method of claim 251 wherein M is R^5-X-;

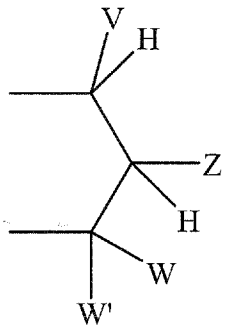
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl,

$-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form a substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} are substituted or unsubstituted groups independently selected from the group consisting of H, lower alkyl, lower aryl, lower aralkyl, wherein any group except H may be substituted, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

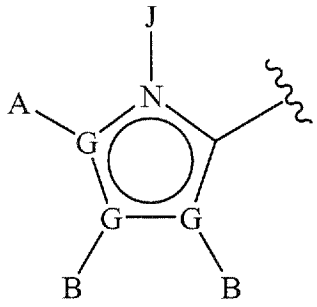
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

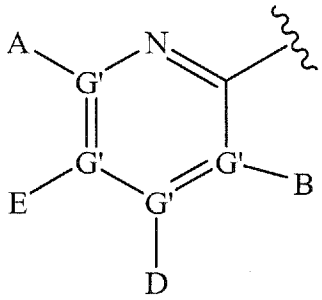
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are substituted or unsubstituted groups independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, wherein any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is substituted or unsubstituted and is selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

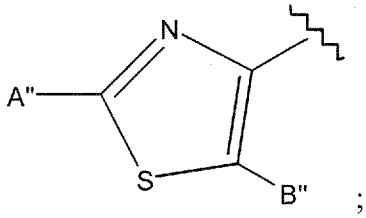
3) when R^5 is a six-membered ring, then X is not any 2 atom linker, a substituted or unsubstituted –alkyloxy-, or ~~asubstituted~~substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

253 (previously presented). The method of claim 252 wherein R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, and halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

254 (previously presented). The method of claim 253 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H, and halo may be substituted.

255 (previously presented). The method of claim 254 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

256 (previously presented). The method of claim 252 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

257 (previously presented). The method of claim 256 wherein X is furan-2,5-diyl.

258 (previously presented). The method of claim 252 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

259 (previously presented). The method of claim 258 wherein both Y groups are -O- and R^1 is H.

260 (previously presented). The method of claim 252 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

261 (previously presented). The method of claim 260 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

262 (previously presented). The method of claim 252 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

263 (previously presented). The method of claim 252 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

264 (previously presented). The method of claim 252 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

265 (previously presented). The method of claim 252 wherein X is furan-2,5-diyl and YR^1 is OH.

266 (previously presented). The method of claim 252, wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

267 (previously presented). The method of claim 252, wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

268 (previously presented). The method of claim 267 wherein X is furan-2,5-diyl.

269 (previously presented). The method of claim 252 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

270 (previously presented). The method of claim 269 wherein X is furan-2,5-diyl.

271 (currently amended). The method of claim 251 wherein said insulin sensitizer is a thiazolidinedione and M is R^5-X-;

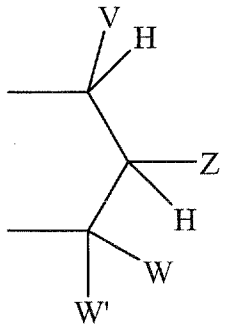
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic

moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, $-alkyl-S-C(O)R^3$, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and $-cycloalkylene-COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

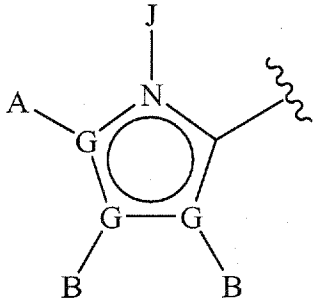
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

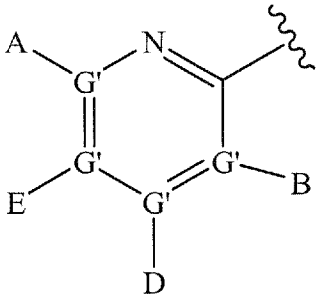
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, -NR^4_2, -$CONR^4_2$, -CO_2R^3, halo, -$S(O)R^3$, -SO_2R^3, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, -CH_2OH, -$CH_2NR^4_2$, -CH_2CN, -CN, -$C(S)NH_2$, -OR^3, -SR^3, -N_3, -$NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, -$C(O)R^{11}$, -$C(O)SR^3$, -SO_2R^{11}, -$S(O)R^3$, -CN, -NR^9_2, -OR^3, -SR^3, perhaloalkyl, halo, -NO_2, and null, provided that any group except –H, -CN, perhaloalkyl, -NO_2, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, -$C(O)OR^3$, -$CONR^4_2$, -CN, -NR^9_2, -NO_2, -OR^3, -SR^3, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with –$COOR^2$, -SO_3H, or –$PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, -NR^2_2, and –OR^2;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

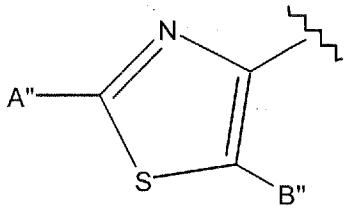
3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,~~alinker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and

R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, or halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

272 (previously presented). The method of claim 271 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H, and halo may be substituted.

273 (previously presented). The method of claim 272 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

274 (previously presented). The method of claim 271 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

275 (previously presented). The method of claim 274 wherein X is furan-2,5-diyl.

276 (previously presented). The method of claim 271 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

277 (previously presented). The method of claim 276 wherein both Y groups are -O- and R^1 is H.

278 (previously presented). The method of claim 271 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

279 (previously presented). The method of claim 278 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

280 (previously presented). The method of claim 271 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

281 (previously presented). The method of claim 271 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

282 (previously presented). The method of claim 271 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

283 (previously presented). The method of claim 271 wherein X is furan-2,5-diyl and YR^1 is OH.

284 (previously presented). The method of claim 271 wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

285 (previously presented). The method of claim 271 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

286 (previously presented). The method of claim 285 wherein X is furan-2,5-diyl.

287 (previously presented). The method of claim 271 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

288 (previously presented). The method of claim 287 wherein X is furan-2,5-diyl.

289 (previously presented). The method of claim 271 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

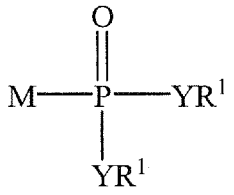
290 (previously presented). The method of claim 251 wherein said insulin sensitizer is a thiazolidinedione.

291-292 (canceled).

293 (previously presented). The method of claim 251 wherein said combination is administered orally.

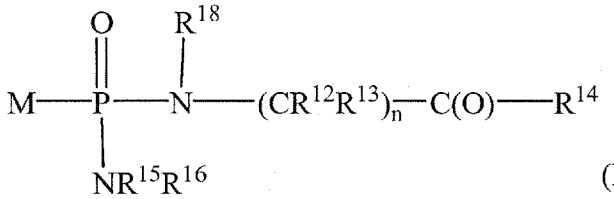
294-298 (canceled).

299 (currently amended). A method of treating insulin resistance comprising administering to patients in need thereof a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrugs or salts thereof, wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA);

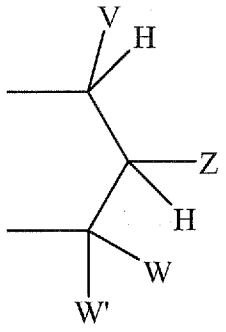
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to $M\text{-}PO_3^{2-}$ which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and $-NR^6-$;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, up to containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower aryl, substituted or unsubstituted lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

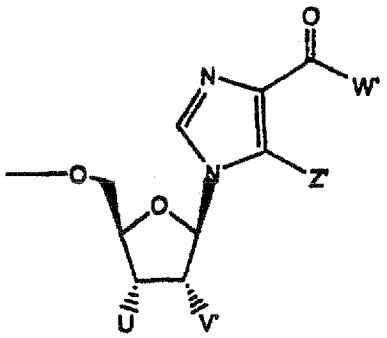
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and:

M is



;

wherein

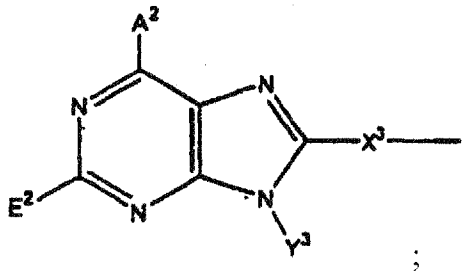
Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino;

and pharmaceutically acceptable salts thereof; or

M is



;

wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of –H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

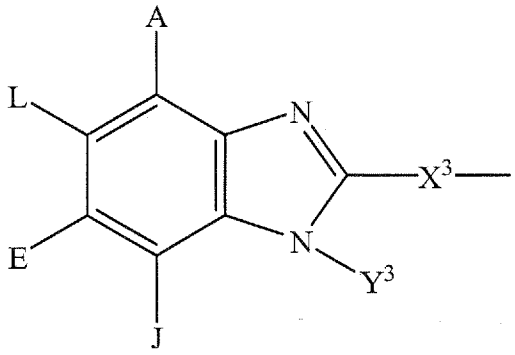
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein:

A, E, and L are selected from the group of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

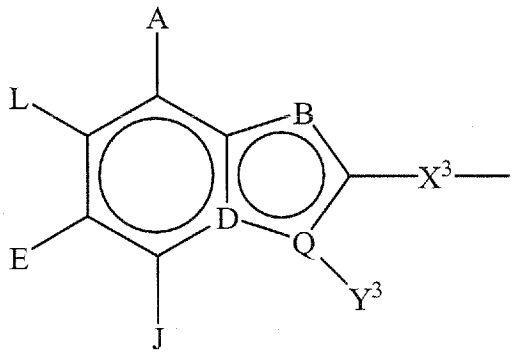
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein

B is selected from the group consisting of –NH-, -N= and –CH=;

D is selected from the group consisting of —C═ and —N— ;

Q is selected from the group consisting of –C= and –N- with the proviso that when B is –NH- then Q is –C= and D is —C═, when B is –CH= then Q is –N- and D is —N— —C═ , when B is –N=, then D is —N— and Q is –C=;

A, E, and L are selected from the group of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H may be substituted;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

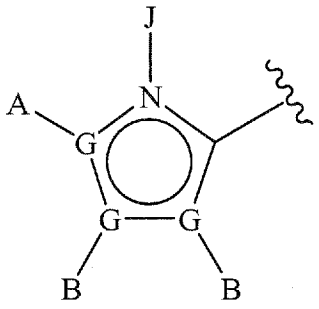
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

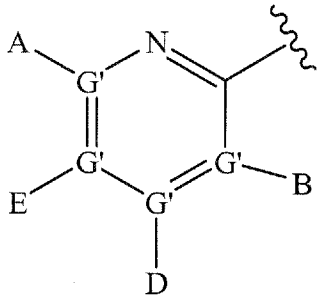
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^3$, and

pharmaceutically acceptable salts thereof; or

M is



or



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that all groups except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that all except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, substituted or unsubstituted –alkyloxy-, or substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

300 (currently amended). The method of claim 299 wherein M is R^5-X-;

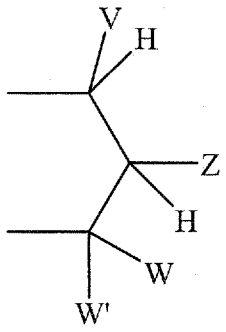
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl,

$-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

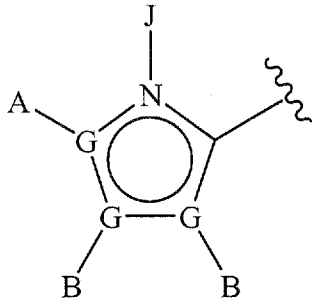
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

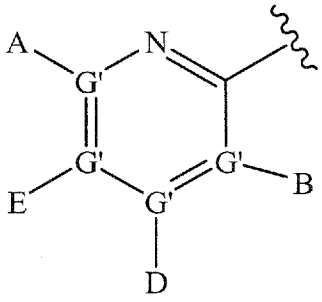
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

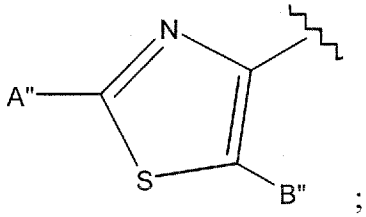
3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,a~~linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

301 (previously presented). The method of claim 300 wherein R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, or halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

302 (previously presented). The method of claim 301 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H, and halo may be substituted.

303 (previously presented). The method of claim 302 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

304 (previously presented). The method of claim 300 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

305 (previously presented). The method of claim 304 wherein X is furan-2,5-diyl.

306 (previously presented). The method of claim 300 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

307 (previously presented). The method of claim 306 wherein both Y groups are -O- and R^1 is H.

308 (previously presented). The method of claim 300 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

309 (previously presented). The method of claim 308 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

310 (previously presented). The method of claim 300 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

311 (previously presented). The method of claim 300 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

312 (previously presented). The method of claim 300 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

313 (previously presented). The method of claim 300 wherein X is furan-2,5-diyl and YR^1 is OH.

314 (previously presented). The method of claim 300 wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

315 (previously presented). The method of claim 300 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

316 (previously presented). The method of claim 315 wherein X is furan-2,5-diyl.

317 (previously presented). The method of claim 300 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

318 (previously presented). The method of claim 317 wherein X is furan-2,5-diyl.

319 (currently amended). The method of claim 299 wherein said insulin sensitizer is a thiazolidinedione and M is R^5-X-;

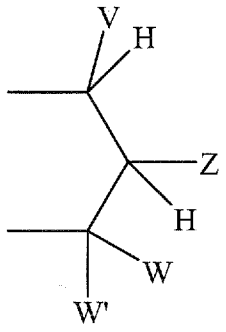
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl,

$-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$,~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

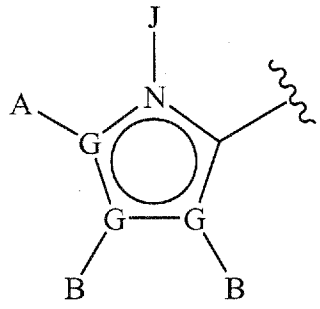
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

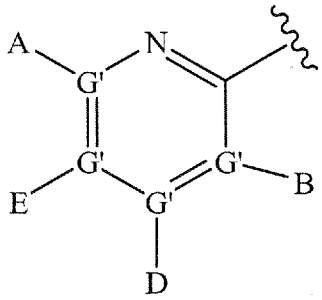
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

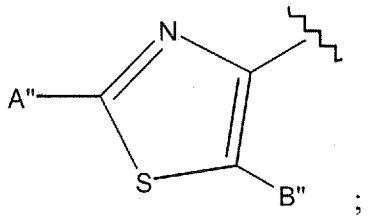
3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,a~~linker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and

R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, or halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

320 (previously presented). The method of claim 319 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H and halo may be substituted.

321 (previously presented). The method of claim 320 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

322 (previously presented). The method of claim 319 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

323 (previously presented). The method of claim 322 wherein X is furan-2,5-diyl.

324 (previously presented). The method of claim 319 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

325 (previously presented). The method of claim 324 wherein both Y groups are -O- and R^1 is H.

326 (previously presented). The method of claim 319 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

327 (previously presented). The method of claim 326 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

328 (previously presented). The method of claim 319 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

329 (previously presented). The method of claim 319 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

330 (previously presented). The method of claim 319 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

331 (previously presented). The method of claim 319 wherein X is furan-2,5-diyl and YR^1 is OH.

332 (previously presented). The method of claim 319 wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

333 (previously presented). The method of claim 319 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

334 (previously presented). The method of claim 333 wherein X is furan-2,5-diyl.

335 (previously presented). The method of claim 319 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

336 (previously presented). The method of claim 335 wherein X is furan-2,5-diyl.

337 (previously presented). The method of claim 319 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

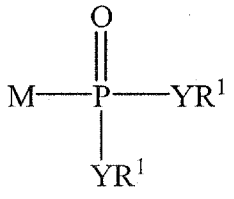
338 (previously presented). The method of claim 299 wherein said insulin sensitizer is a thiazolidinedione.

339-340 (canceled).

341 (previously presented). The method of claim 299 wherein said combination is administered orally.

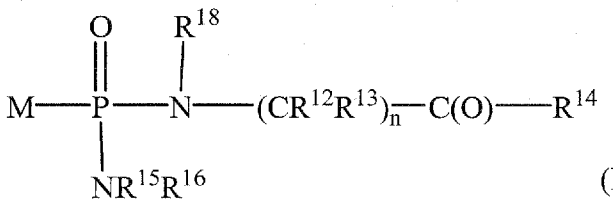
342-346 (canceled).

347 (currently amended). A method of treating a disease or condition selected from the group consisting of hyperlipidemia, atherosclerosis, ischemic injury, hypertension, and hypercholesterolemia which comprises administering to an animal in need thereof a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrugs or salts thereof, wherein said FBPase inhibitor is a compound selected from the group consisting of formulae I and IA:



(I)

and



(IA);

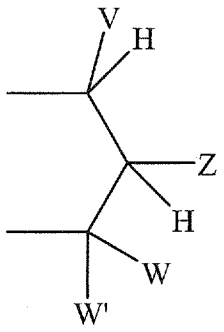
wherein *in vivo* or *in vitro* compounds of formulae I and IA are converted to M-PO_3^{2-} which inhibits FBPase and wherein

Y is independently selected from the group consisting of -O-, and -NR^6-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, -$C(R^2)_2OC(O)NR^2_2$, -NR^2-C(O)-R^3, -$C(R^2)_2$-OC(O)R^3, -$C(R^2)_2$-O-C(O)OR^3, -$C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is -NR^6-, then R^1 attached to -NR^6- is independently selected from the group consisting of -H, -$[C(R^2)_2]_q$-$COOR^3$, -$C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q$-C(O)SR$_3$~~ and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, up to containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower aryl, substituted or unsubstituted lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

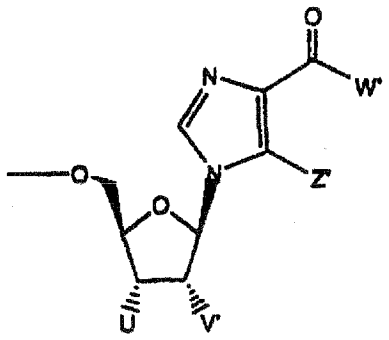
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$ and:

M is



;

wherein

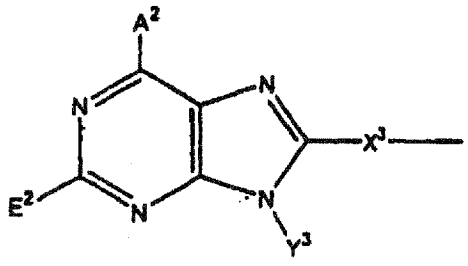
Z' is selected from the group consisting of alkyl or halogen,

U and V' are independently selected from the group consisting of hydrogen, hydroxy, acyloxy or when taken together form a lower cyclic ring containing at least one oxygen;

W' is selected from the group consisting of amino and lower alkyl amino;

and pharmaceutically acceptable salts thereof; or

M is



;

wherein

A^2 is selected from the group consisting of $-NR^8_2$, $NHSO_2R^3$, $-OR^5$, $-SR^5$, halogen, lower alkyl, $-CON(R^4)_2$, guanidine, amidine, -H, and perhaloalkyl;

E^2 is selected from the group consisting of –H, halogen, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

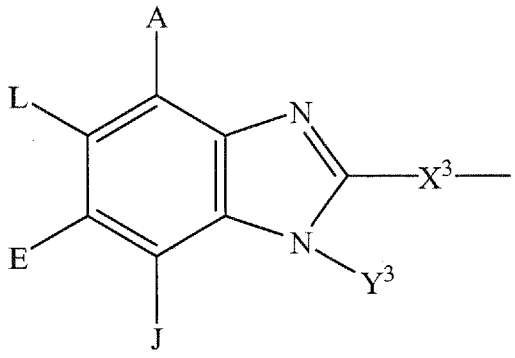
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein:

A, E, and L are selected from the group of $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$;

each R^4 is independently selected from the group consisting of –H and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

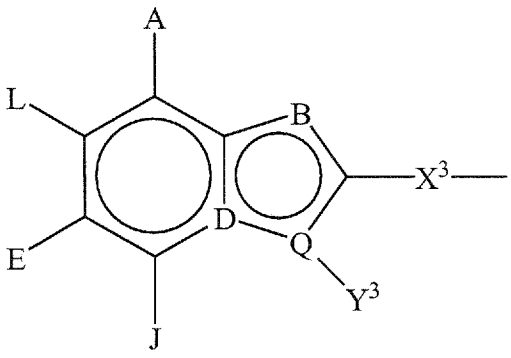
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2{}_2$, and $-OR^2$, and

pharmaceutically acceptable salts thereof; or

M is:



;

wherein

B is selected from the group consisting of –NH-, -N= and –CH=;

D is selected from the group consisting of $-\overset{|}{C}=$ and $-\overset{|}{N}-$;

Q is selected from the group consisting of –C= and –N- with the proviso that when B is –NH- then Q is –C= and D is $-\overset{|}{C}=$, when B is –CH= then Q is –N- and D is $-\overset{|}{N}-$ $\underline{-\overset{|}{C}=}$, when B is –N=, then D is $-\overset{|}{N}-$ and Q is –C=;

A, E, and L are selected from the group of $-NR^8{}_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4{}_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or

together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, –H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y forms a cyclic group including aryl, cyclic alkyl, and heterocyclic alkyl;

X^3 is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkyl-, alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is H or a substituted or unsubstituted group selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H may be substituted;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from the group consisting of –H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

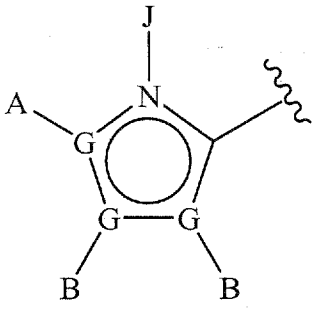
R^8 is independently selected from the group consisting of –H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidendate alkyl;

R^{10} is selected from the group consisting of –H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

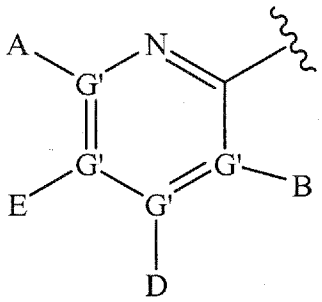
R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^3$, and

pharmaceutically acceptable salts thereof; or

M is



or



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that all groups except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that all except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is substituted or unsubstituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom linker, substituted or unsubstituted –alkyloxy-, or substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

348 (currently amended). The method of claim 347 wherein M is R^5-X-;

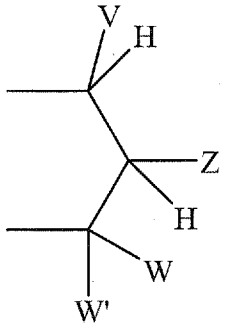
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl,

$-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR$~~, and -cycloalkylene-$COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

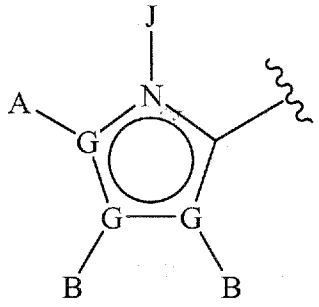
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~aralkyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

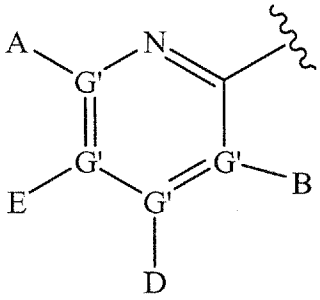
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

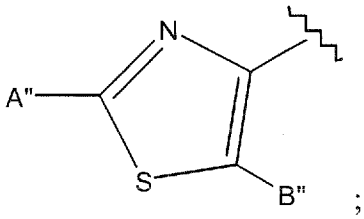
3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,~~alinker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups;

and pharmaceutically acceptable salts thereof.

349 (previously presented). The method of claim 348 wherein R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, or halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

350 (previously presented). The method of claim 349 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and wherein any group except -H and halo may be substituted.

351 (previously presented). The method of claim 349 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

352 (previously presented). The method of claim 348 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

353 (previously presented). The method of claim 352 wherein X is furan-2,5-diyl.

354 (previously presented). The method of claim 348 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

355 (previously presented). The method of claim 354 wherein both Y groups are -O- and R^1 is H.

356 (previously presented). The method of claim 348 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

357 (previously presented). The method of claim 356 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

358 (previously presented). The method of claim 348 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

359 (previously presented). The method of claim 348 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

360 (previously presented). The method of claim 348 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

361 (previously presented). The method of claim 348 wherein X is furan-2,5-diyl and YR^1 is OH.

362 (previously presented). The method of claim 348, wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

363 (previously presented). The method of claim 348, wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

364 (previously presented). The method of claim 363 wherein X is furan-2,5-diyl.

365 (previously presented). The method of claim 348 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

366 (previously presented). The method of claim 365 wherein X is furan-2,5-diyl.

367 (currently amended). The method of claim 347 wherein said insulin sensitizer is a thiazolidinedione and M is R^5-X-;

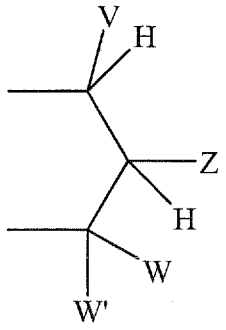
Y is independently selected from the group consisting of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group consisting of -H, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alicyclic where the cyclic

moiety contains a carbonate or thiocarbonate, substituted or unsubstituted -alkylaryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, $-alkyl-S-C(O)R^3$, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6-$, then R^1 attached to $-NR^6-$ is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, ~~$-[C(R^2)_2]_q-C(O)SR_3$~~ and $-cycloalkylene-COOR^3$;

or when either Y is independently selected from -O- and $-NR^6-$, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



,

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms and up to 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, containing up to 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an substituted or unsubstituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, containing up to one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, containing 0–2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from the group consisting of H, lower alkyl, aryl, aralkyl, or together with R^{12} is connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and R^{13} is H or a substituted or unsubstituted group independently selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, or R^{12} and R^{13} together are connected via 2-6 carbon atoms to form a cyclic group;

each R^{14} is independently selected from the group consisting of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, and $-SR^{17}$;

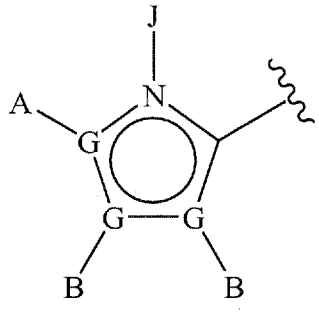
R^{15} is selected from the group consisting of –H, lower alkyl, lower aryl, lower ~~arakyl~~aralkyl, or together with R^{16} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

R^{16} is selected from the group consisting of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

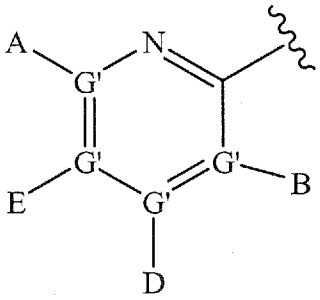
each R^{17} is independently selected from the group consisting of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, including up to 1 heteroatom selected from the group consisting of O, N, and S;

with the proviso that when only one Y is –O-, and it is not part of a cyclic group containing the other Y, then the other Y must be $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14} and

R^5 is selected from the group consisting of:



and



;

wherein:

each G is independently selected from the group consisting of C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N;

each G' is independently selected from the group consisting of C and N and wherein no more than two G' groups are N;

A is selected from the group consisting of –H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, -NHAc, and null;

each B and D are a substituted or unsubstituted group independently selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, provided that any group except –H, -CN, perhaloalkyl, $-NO_2$, and halo may be substituted;

E is a substituted or unsubstituted group selected from the group consisting of –H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4_2$, -CN, $-NR^9_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, provided that any group except –H, -CN, perhaloalkyl, and halo may be substituted;

J is selected from the group consisting of –H and null;

X is a substituted or substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom,

and wherein X is a substituted or unsubstituted group selected from the group consisting of –alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, alkyloxy-, -alkylthioalkyl-, -alkylthio-, alkylaminocarbonyl-, alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and –alkylaminocarbonylamino-, with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

R^2 is selected from the group consisting of R^3 and –H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group consisting of –H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

each R^9 is independently selected from the group consisting of –H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group consisting of alkyl, aryl, $-NR^2_2$, and $-OR^2$;

and with the proviso that:

1) when G' is N, then the respective A, B, D, or E is null;

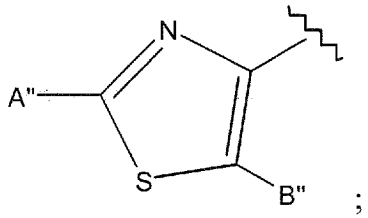
2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of –H or null;

3) when R^5 is a six-membered ring, then X is not any 2 atom ~~linker,~~alinker, a substituted or unsubstituted –alkyloxy-, or a substituted or unsubstituted –alkylthio-;

4) when G is N, then the respective A or B is not halogen or a group directly bonded to G via a heteroatom; and

5) when X is not a –heteroaryl- group, then R^5 is not substituted with two or more aryl groups; and

R^5 is



;

A'' is of -H, $-NR^4_2$, $-CONR^4_2$, $-CO_2R^3$, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C1-C6 perhaloalkyl, C_1-C_6 haloalkyl, aryl, $-CH_2OH$, $-CH_2NR^4_2$, $-CH_2CN$, -CN, $-C(S)NH_2$, $-OR^3$, $-SR^3$, $-N_3$, $-NHC(S)NR^4_2$, and –NHAc;

B'' is a substituted or unsubstituted group selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9_2$, $-OR^3$, $-SR^3$, perhaloalkyl, or halo, wherein any group except -H, -CN, perhaloalkyl, and halo may be substituted.

368 (previously presented). The method of claim 367 wherein A" is $-NH_2$, -Cl, -Br, or $-CH_3$; B" is a substituted or unsubstituted group selected from –H, $-C(O)OR^3$, $-C(O)SR^3$, C_1-C_6 alkyl, $C(O)R^{11}$, alicyclic, halo, heteroaryl, or $-SR^3$ and all except -H, and halo may be substituted.

369 (previously presented). The method of claim 368 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl.

370 (previously presented). The method of claim 367 wherein X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

371 (previously presented). The method of claim 370 wherein X is furan-2,5-diyl.

372 (previously presented). The method of claim 367 wherein when both Y groups are -O-, then R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted benzyl, $-C(R^2)_2OC(O)R^3$, $-C(R^2)_2OC(O)OR^3$, and -H.

373 (previously presented). The method of claim 372 wherein both Y groups are -O- and R^1 is H.

374 (previously presented). The method of claim 367 wherein when Y is NR^6, R^6 is selected from H, lower alkyl, acyclooxyalkyl, alkoxycarbonylalkyl, or lower acyl; and R^1 is independently selected from the group consisting of -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR^3$, and -cycloalkylene-$COOR^3$, wherein R^4 is, independently, alkyl or H and R_3 is alkyl, aryl, alicyclic or aralkyl.

375 (previously presented). The method of claim 374 wherein Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

376 (previously presented). The method of claim 367 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

377 (previously presented). The method of claim 367 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and YR^1 is OH.

378 (previously presented). The method of claim 367 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

379 (previously presented). The method of claim 367 wherein X is furan-2,5-diyl and YR^1 is OH.

380 (previously presented). The method of claim 367, wherein X is furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

381 (previously presented). The method of claim 367, wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; and YR^1 is OH.

382 (previously presented). The method of claim 381 wherein X is furan-2,5-diyl.

383 (previously presented). The method of claim 367 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl; Y is NR^6 and R^6 is H; and R^1 is $-C(R^4)_2COOR^3$, wherein R^4 is, independently, H or methyl; and R^3 is alkyl.

384 (previously presented). The method of claim 383 wherein X is furan-2,5-diyl.

385 (previously presented). The method of claim 347 wherein said thiazolidinedione is selected from the group consisting of BRL 49653, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, GI-262570, SB219994, SB219993, and darglitazone.

386 (previously presented). The method of claim 347 wherein said insulin sensitizer is a thiazolidinedione.

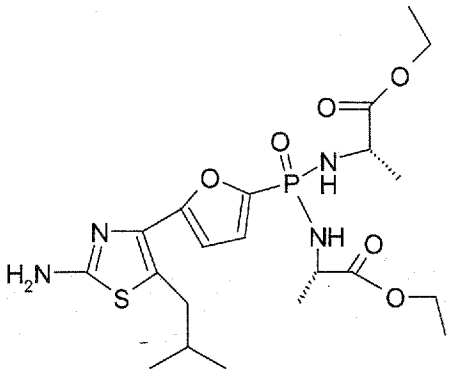
387-388 (canceled).

389 (previously presented). The method of claim 347 wherein said combination is administered orally.

390-394 (canceled).

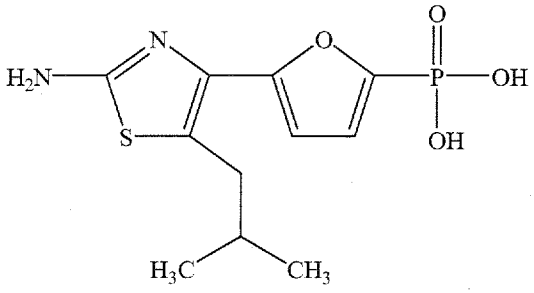
395 (previously presented). The method of claim 224 wherein A" is $-NH_2$; B" is a C_1-C_6 alkyl or $C(O)R^{11}$, wherein R^{11} is alkyl; and X is selected from the group consisting of methylenoxycarbonyl and furan-2,5-diyl.

396 (previously presented). The method of claim 299 wherein said FBPase inhibitor is



Compound J

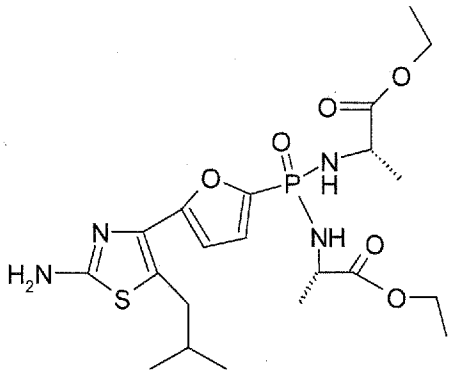
or



Compound H

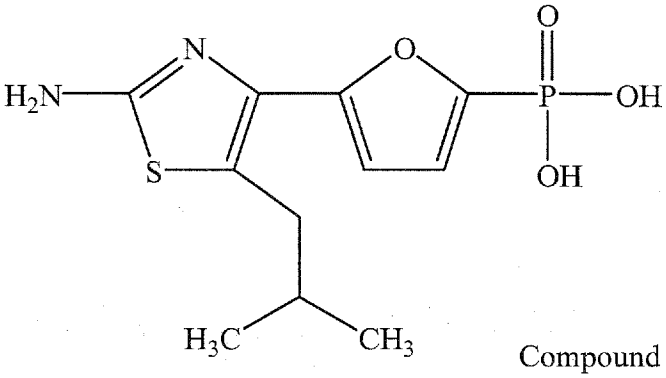
and said insulin sensitizer is troglitazone.

397 (previously presented). The method of claim 347 wherein said FBPase inhibitor is



Compound J

or



Compound H

and said insulin sensitizer is troglitazone.